ISSN 1391-0736

The Sri Lanka Prescriber

December 2013; Volume 21, No. 4

CONTENTS

The Sri Lanka Prescriber *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.*

The Sri Lanka
Prescriber

Copies of the *Sri Lanka Prescriber* and inquiries from M. P. Kuruppu, Deputy General Manager, Marketing, and Ms Anusha Gunatilleke, Manager Promotions and Publicity (Telephone 2338102), State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

Published by

Department of Pharmacology
Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315
E-mail: phrm_cmb@hotmail.com
and
State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1.
Telephones + 94 11 2320356-9
Fax: + 94 11 447118
E-mail: prmanager@spc.lk Web site: www.spc.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2435975
E-mail: anpress@sltnet.lk

Cover picture

THE SOCIETY OF APOTHECARIES
(1617 A.D.)

English apothecaries of the Middle Ages were dominated by the Guild of Grocers. In 1617, after much controversy, King James I granted a separate charter to The Society of Apothecaries of London, first Anglo-Saxon pharmaceutical organization.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Pharmacokinetics and pharmacodynamics of antibiotics: relevance in clinical practice

The germ theory of disease based on the work of Louis Pasteur and Robert Koch, links specific microorganisms to diseases. Many factors affect treatment outcome of infectious disease including host defense mechanisms, site of infection, virulence of the pathogen and pharmacological properties of the antibiotic given to treat an infection. Of these, the main factors responsible for appropriate prescription by clinicians are choice and dose of antibiotics.

In most instances the dose of antibiotics is based more on habit than on science.Yet, knowledge of their pharmacokinetic properties, pharmacodynamic aspects, and mode of action can refine drug selection and dosing regimens. Such selection would lead to maximum therapeutic effect with minimum toxicity and cost.

Pharmacokinetics is the study of the movements of a medicine from its site of administration to the place of its pharmacologic activity and its elimination from the body. Pharmacodynamics is the study of what medicines do to the body. Aspects of such processes regarding antibiotics are discussed in this article.

Pharmacokinetic basis for antibiotic treatment

In many infections the offending pathogen causes disease in a specific organ or only in a specific pathological compartment within an organ. Antibiotics are usually administered far away from sites of infection, and to effectively inhibit growth or kill bacteria, they need to penetrate into the target site in sufficient concentration. When selecting an antibiotic, a crucial consideration is whether it can reach the site of infection.This would depend on physical barriers the molecule must cross, chemical properties of the drug, and presence of multidrug transporters. Poor penetration into an infected anatomical compartment is likely to cause treatment failure. Hence it is important to select an antibiotic that can penetrate certain infected anatomical compartments such as vitreous humour of the eye, and the cerebrospinal fluid.

Pharmacokinetic properties of an antibiotic determine its concentration at the site of infection, which in turn is reflected by the serum concentration profile over time (See panel 1).

Panel 1. Factors affecting pharmacokinetics of medicines

1. Release from dosage form
2. Absorption from site of administration to blood stream
3. Distribution to various parts of body
4. Rate of elimination from body

The rate and extent of absorption of a medicine determine its bioavailability and appropriate route of administration. Bioavailability is considered 100% when a medicine is administered intravenously (IV). For drugs such as cephalexin, levofloxacin and ciprofloxacin bioavailability is >90% even when administered orally. A high bioavailability following oral administration often permits inexpensive but effective treatment of infection without using injectables or hospitalisation. A major advantage of replacing IV antibiotics with oral preparations is avoidance of IV line sepsis. Replacing IV antibiotics with oral formulations is not recommended for antibiotics given orally having <50% bioavailability.

The volume of distribution (V) measures the extent of drug distribution in the body tissues and fluids. A small V indicates that medicine is confined to plasma or extracellular fluid (ECF) (eg. aminoglycosides, cephalosporins), whereas a large V indicates an extensive distribution to tissues (eg. azithromycin). Volume of distribution of medicine can vary between

patient populations such as neonates or adults, and also from person to person in the same population. Such variation is due to individual differences in physiology and presence of comorbid disease. Volume of distribution helps to determine dose of medicine needed to produce a desired plasma concentration. In clinical practice V is used to calculate loading dose and to determine suitability for removal by dialysis.

Clearance, a drug specific property, is the capacity of the eliminating organ to metabolise and eliminate a medicine. It depends on the intrinsic capacity of the organ to remove a medicine and on the blood flow to the eliminating organ. Clearance can vary between individuals due to age, comorbidities and concomitant use of other medicines. Dose reduction or change in dosing frequency depends on whether disease has affected the function and blood supply of organs excreting the medicine. In such circumstances the maintenance dose regimen should be suitably changed. For example, the dose of aminoglycosides is reduced and the dosing interval is increased in people with renal impairment. Alternatively, an antibiotic eliminated by another organ such as the liver may be prescribed.

Pharmacodynamic basis for antibiotic therapy

Antibiotics inhibit growth or cause death of bacteria by binding to specific bacterial structures or proteins. To be effective an antibiotic must occupy an adequate number of binding sites (ie. concentration), and should remain at the site for a sufficient time for appropriate antibacterial activity. Only the free concentration of an antibiotic will exhibit antibacterial activity.

Integration of how high (concentration) and how long (time) an antibiotic level remains above zero concentration over a dosing interval is referred to as area under the plasma concentration-time curve (AUC). The AUC measures concentration of medicine over a given time period and reflects the amount of exposure of bacteria to the antibiotic over a dosing interval.

Pattern of bacterial killing

The pattern of bacterial killing is either time-dependent or concentration-dependent.

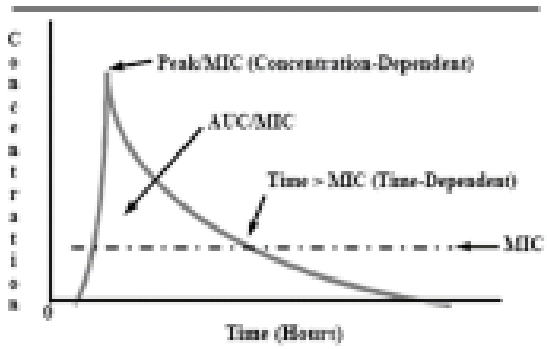

Figure 1. *PK/PD parameters affecting antibiotic potency.*

(Source: http://www.medscape.com/viewarticle/479024)

Minimum inhibitory concentration (MIC) is the lowest serum concentration of an antibiotic that will inhibit visible growth of bacteria after an overnight incubation. When bacterial killing is time-dependent, duration that the antibiotic concentration remains above the MIC for bacteria in any one dosing interval becomes the best predictor of clinical outcome. Serum levels of such antibiotics should remain above MIC of the target pathogen for at least 40% - 50% of dosing interval to ensure an optimum degree of bacterial eradication. Once concentration exceeds a critical value, which appears to be about 2 to 4 times above MIC for an organism, bacterial killing proceeds at a zero order rate. Increasing drug concentration beyond this does not increase microbial death rate.

If concentration-dependent, bacterial killing depends on the antibiotic concentration at the site of infection, and this should be greater than MIC for the organism. Increasing antibiotic concentration up to a specific level increases rate of bacterial eradication resulting in dose dependent bacterial killing. Increasing beyond this concentration will not increase the rate of bacterial killing. If concentration is high enough, most bacteria die within a short time and the effect of duration of exposure to medicine is minimal. For such antibiotics the best

response occurs when concentrations are at least 10 times the MIC for the target organism at the site of infection. This is the basis for using a loading dose for such antibiotics. Loading dose will also reduce tissue accumulation and thereby minimise risks of adverse effects of antibiotics. Persistent suppression of antibacterial growth following antimicrobial exposure (post-antibiotic effect) also occurs with antibiotics showing concentration-dependent killing. This reduces the number of doses needed to achieve effective antibacterial activity (See panel 2).

Panel 2. Commonly used antibiotics according to type of bacterial killing

Time-dependent killing	Concentration-dependent killing
• β-Lactams	• Aminoglycosides
• Macrolides	• Azithromycin
• Clindamycin	• Fluoroquinolones
	• Vancomycin

Pharmacokinetic/pharmacodynamic (PK/PD) break points of antibiotics

MIC is an in vitro method to measure susceptibility of bacteria to antibiotics. In contrast to using only MIC, PK/PD based methods reflect in vivo conditions and are more predictive of antibiotic efficacy. PK/PD break point (susceptibility limit) of an antibiotic is the antibacterial concentration calculated from a PD parameter and the dimension of such parameter which predicts efficacy in vivo. Break points are used to define susceptibility and resistance, and help in defining dosage regimens capable of achieving the desired concentration of an antibiotic.

PK/PD break point for antibiotics showing time-dependent killing is the serum concentration above MIC present for >40-50% of dosing interval. When MIC is below break point, an organism is considered as susceptible to the given antibiotic and resistant if it is above. For concentration-dependent killing, the major parameter that defines clinical and bacteriological efficacy is ratio of 24 hour AUC to MIC. This should be >25% for less severe infections and immunocompetent hosts, and >100% for severe infections and immunocompromised hosts. PK/PD breakpoints for concentration-dependent agents can be calculated from the formula AUC/25 or AUC/100.

Conclusions

PK and PD characteristics determine efficacy of antibiotic treatment. Knowledge of PK and PD helps clinicians to select the most appropriate antibiotic regimen for an infection of a particular patient. This knowledge would reduce use of inappropriate antibiotics, emergence of bacterial resistance, and cost of treatment.

Further reading

1. Jacobs MR. Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. *Clinical Microbiology and Infections* 2001; **7**: 589-96.
2. Quintiliani R. Using pharmacodynamic and pharmacokinetic concepts to optimize treatment of infectious diseases.http://www. medscape. com/viewarticle/479024
3. Turnidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. *Clinical Microbiology Reviews* 2007; **20**: 391-408.
4. Ahern JW, Pierce KK. Pharmacokinetics: Practical application to antimicrobial therapy. *Infectious Diseases in Clinical Practice* 2011; **19**: 16-24.

Dr Chandanie Wanigatunge MBBS, MD, FCCP, *Senior Lecturer in Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.*

Email: caw@sjp.ac.lk

Competing interests: None

Management of behaviour disorders in children

Problem behaviours are common in children. Disorders of behaviour differ from these common problems by being more intensive, burdensome and persistent. They have an adverse effect on the child's emotional and functional wellbeing, and on others associated with the child, including parents, siblings, peers and teachers. Behaviour disorders are poorly understood by parents and others. They are given various explanations based on cultural and social beliefs. As a result, children and families are often denied much needed early intervention. Untreated disorders persist and are harder to change in an older child or adolescent.

Under the broad umbrella of behaviour disorders, accepted diagnostic classifications identify different types according to their main clinical features. "Oppositional defiant disorder" (ODD), "conduct disorder" (CD) and "attention deficit hyperactivity disorder" (ADHD) are some diagnostic labels. Maladaptive behaviours common to all these disorders are hostility and aggression, temper tantrums, disruptive and destructive behaviour, defiance of adult authority, irritability and low tolerance for frustration. These are the behaviours that motivate the adult care givers to seek help. These behaviours are also present in other conditions in children, which are equally burdensome and need different management. These are intellectual impairment, developmental disorders such as autism, learning difficulties, neurological disorders, mood disorders, anxiety, difficult temperament and disrupted family environment.

The content of this article is restricted to management of behaviour disorders in children 5 to 12 years of age. The preschool and adolescent age groups are somewhat different in the underlying risk factors and presentation of behaviour, so require separate attention. The object here is to outline principles of management of conditions with the above mentioned problem behaviours and associated symptoms, rather than discuss individual disorders.

Assessment of behaviour

Engaging parents in providing systematic and accurate information is important from the outset. At the time they seek medical help parents often feel helpless and are intimidated by their child's behaviour, having tried and failed in managing them. Often, the methods adopted by parents also result in reinforcing the difficult behaviour. Information obtained from parents should include (i) a description of behaviour the parents consider as difficult (ii) settings in which such behaviour occurs (iii) triggers for such behaviour, and (iv) methods tried by parents to settle the child. For example, if the parent does not give immediate attention to a child's request he will lose temper, throw things, falls on the floor and continuously screams. Parents give in to calm him down. Such behaviour problems are seen in the presence of parents but never in school. These details are useful in understanding the pattern of behaviour and adopting preventive measures. A useful tool to gather information is to get the parents to maintain a diary of antecedents, the behaviour and consequences (ABC of behaviour). Other useful sources of information are the schoolteachers who can provide information related to learning abilities, classroom behaviour, peer interaction and compliance with routines and rules in the classroom.

It is important to identify other conditions that make a child more vulnerable to a behaviour disorders. These are learning difficulties, developmental delay, neurological problems such as epilepsy, and past cerebral infections and traumatic brain injury. Predispositions include premature birth, low birthweight and a family history of violence. Children with more serious behaviour disorders such as conduct disorder are recognised from the additional presence of insensitivity to others, cruelty to animals, fire setting, stealing and lying. Information equally important to management are the factors that maintain difficult behaviour, such as physical punishment, chaotic and conflict-ridden family environment, and unskilled parenting.

Several standardised assessment tools are available to screen inattention, hyperactivity, impulsiveness, antisocial behaviour, emotional problems and relationship difficulties. Underlying basis for learning difficulties can be assessed using standardised tools for measuring intelligence and cognitive skills. At the end of assessment, sharing the composite clinical formulation will help parents to understand the multiple facets of the child's problem rather than focus on few individual behaviours.

Risk assessment

Risk assessment is important in view of the serious short and long term consequences of behaviour disorders in children. The aim is to identify risks already present or with a high potential to occur, such as educational failure, social rejection by peers or from school, harm to others, harm to self, or risk of receiving harsh punishments. For example, a child with ADHD is at risk of early school drop-out, being physically abused, and is prone to unintentional injury.

Parent education

Parents play an important role in management, but often their expectation is to receive medication for a quick-fix solution to the problem. Hence education about the problem and involving them in setting targets for management is important from the beginning. Parents also need guidance to arrive at realistic expectations of outcome. Risk assessment is a useful guide here to identify priorities for management and in taking preventive measures.

Parents look for possible causes of the problem and have their own explanations, yet a valid cause is difficult to find, specially because these behaviours are usually present from early childhood and multiple factors contribute to persistence over time. Also, parents often feel the child deliberately behaves in ways to challenge them. On the contrary, child is the victim of his own lack of skills to manage frustration, emotional arousal and behaviour, and needs parental help to remedy them. In addition to clarifying misconceptions, parents need direct and honest information in simple understandable language about the nature of the child's problem and how they should contribute to management.

Psychosocial intervention

Intervention with parents in general involves in helping them develop better and more effective parenting skills. Physical punishments may have short term success in containing the child's behaviour, but evidence shows that it is detrimental in the long term. Parenting skills training involves empowering them to set firm and consistent limits on the child's behaviour. Clear, precise communication of expected behaviour is a valuable tool in establishing authority. Limit setting should go hand-in-hand with noticing and verbally acknowledging good behaviour combined with a reward where possible. Predictable daily routines are easier for children to comply with than over-flexible, constantly changing ones.

Intervention with children involves helping them learn appropriate behaviour in their relationships with adults and other children, and in different social settings. A range of evidence based methods are known for social skills training and include individual and group based methods. Anger management training is used to encourage recognition of early signs of emotional arousal and learning effective methods to prevent loss of control. Improving academic learning and other school-based skills would help to prevent early school drop-out.

Use of medication

Medication is used in the management of several concurrent disorders and symptoms in children with behaviour disorders. Recommended doses for age and guidelines for managing side-effects should be followed. Use of multiple drugs should be avoided as far as possible. Starting with a low dose is recommended and abrupt stopping should be avoided to prevent withdrawal or rebound worsening of behaviour.

Methylphenidate 0.7-1 mg/kg/day is used in controlling symptoms of ADHD (hyperactivity, inattention, impulsiveness). Reduced appetite is the commonest side-effect. Weight, blood pressure and heart rate need regular monitoring.

Second generation antipsychotics are useful in controlling anger and aggression. Ones that can be used in children are aripripazole 2.5 - 5 mg and

risperidone 0.5-1mg. Weight gain and risk of metabolic syndrome occur with risperidone.

Other antipsychotics include haloperidol 0.75 - 3 mg once or twice a day. Extrapyramidal side-effects should be carefully monitored. Benzhexol 1-2 mg can be used to counteract side-effects.

Mood stabilisers are commonly used in anger and aggression that is more severe and persistent. Carbamazepine 100-200 mg, sodium valproate 100-200 mg and lamotrigine 50-100 mg are possible choices. Lithium carbonate, though considered the best anti-aggression drug, is best avoided in children because of the side-effects.

Summary

Behaviour disorders in children should be recognised early and managed, in view of their tendency to persist if untreated, and their high social and economic cost. Management should include not only the problem behaviour but also the associated learning difficulties, and improving social skills. The parents are essential partners in the management and should be supported. Medication is useful under certain circumstances but need careful monitoring.

Further reading

1. Murray J, Farrington DP. Risk factors for conduct disorder and delinquency: key findings from longitudinal studies. *The Canadian Journal of Psychiatry* 2010; **55**: 633-42.
2. Connolly A, Vance A. Psychosocial factors associated with parent and teacher reports of aggression in children and adolescents with attention deficit hyperactivity disorder. *Australia and New Zealand Journal of Psychiatry* 2010; **44**: 997-675.
3. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry* 2006; **47**: 276-95.
4. Rosato NS, Corell CU, Pappandopulos E, Chait A, Crystal S, Jensen PS. Treatment of maladaptive aggression in youth: CERT Guidelines II. Treatment and on-going management. *Pediatrics* 2012; **129**: e1577-e1586.

Professor Hemamali Perera MBBS, MD, FRCPsych, *Professor in Psychological Medicine, University of Colombo.*

Email: hemamali_p@yahoo.com

Competing interests: None declared.

Statins in older adults

Summary

Statin use in people over 65 years of age is high.

A meta-analysis of older patients included in randomised trials found good evidence that statins reduce vascular events and mortality in people with existing coronary heart disease.

In older adults, exposure to higher doses of statins or higher potency statins does not increase their effectiveness, but does increase the risk of adverse effects such as myopathy and cognitive impairment.

Increasing age is a risk factor for adverse events with statins. Older patients may be less resilient to these effects.

Older patients may have more comorbidities and be taking more concomitant drugs than the study populations in statin trials. Applying the evidence for statins to older individuals therefore requires frequent review and consideration of the therapeutic goals and potential benefits and harms.

Key words: ageing, deprescribing, HMG CoA reductase inhibitors, myopathy

(Aust Prescr 2013;36:79-82)

Introduction

Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) are the most commonly used cholesterol-lowering drugs. They are being taken by more than 40% of Australians over 65 years of age.[1] Although the prevalence of statin use increases with age, the balance between evidence of their benefits and the risk of adverse effects such as myopathy or impaired cognition may change. In extreme old age, preserving function and avoiding frailty and injury in the short term may become more important than longer term goals such as preventing future cardiovascular events or even extending life.

Efficacy of statins

Older people have an increased risk of cardiovascular disease. However, epidemiological studies suggest that the relative risk for coronary heart disease associated with high cholesterol decreases with age.[2] In addition, in old age, there is an inverse relationship between high cholesterol and the risk of stroke[3] and there are conflicting data on the relationship between high cholesterol and non-cardiovascular mortality.

Cardiovascular events

Statins are most beneficial for preventing cardiovascular events in patients who already have coronary heart disease. A meta-analysis of patients with existing disease (aged 65-82 years) found that all-cause mortality was significantly lower with statins than with placebo (15.6% vs 18.7%) over five years.[4] This equates to a number needed to treat of 28 over five years to save one life. Approximately 25% of patients in the trials were female. Frail older patients may have been excluded because of comorbidity or organ dysfunction.

The role of statins in primary prevention of cardiovascular disease in older people is unclear. Their effects seem to increase over five years, with only minimal benefits over placebo seen in the first year.[5] It is therefore important to consider the patient's probable lifespan when deciding whether to start or continue a statin.

Studies of secondary prevention in patients with cerebrovascular disease suggest that statins are associated with a decrease in recurrent ischaemic stroke but an increase in haemorrhagic stroke.[5]

Other clinical outcomes

There are very limited data assessing the impact of statins on other outcomes such as frailty, physical and cognitive function and institutionalisation. Epidemiological data suggest that statins are not associated with an increase in the risk of developing frailty.[6] This is a condition of increased vulnerability to external stressors and an independent risk factor for adverse clinical outcomes. Symptoms and signs of frailty include complaints of fatigue, unintentional weight loss and low grip strength. We recently

investigated the relationship between statins and institutionalisation and mortality, according to frailty in community-dwelling men aged 70 years and over. There was no association between statin use and institutionalisation or death in older men. Statins did not appear to improve mortality or delay institutionalisation.[7]

Observational studies report conflicting results on the association of statins and muscle mass, strength and function. Results of randomised trials on the effects of statins on cognition are conflicting.[8] In patients with dementia, statins do not significantly affect cognitive decline, global function, behaviour or activities of daily living.[9] A recent pilot study of statin withdrawal showed that statin reduction is associated with improvements in cognitive function in patients with Alzheimer's disease. Moreover, rechallenge with statins was associated with a decline in cognition function.[10]

Statin dose

Meta-analyses suggest that 80% of the lipid-lowering effect of statins occurs at half the maximal statin dose.[11] In older patients, the efficacy of statins for secondary prevention of acute myocardial infarction and death appears to be a class effect, with no difference observed between high or low potency statins.[12] Surrogate markers, such as low density lipoprotein cholesterol, should be interpreted with care in older people. Epidemiological data indicate that lowering low density lipoprotein cholesterol has a smaller impact on the relative risk of coronary heart disease as age increases.[11]

Adverse effects of statins

Adverse effects appear to vary between types and doses of statins. The risk of common events such as myopathy and liver enzyme elevations increases with statin potency and exposure. The degree of statin exposure (area under the concentration–time curve) depends on dose, drug interactions and patient factors including genetic polymorphisms. With ageing, there is a decrease in body size, particularly in muscle mass, and in hepatic and renal function, so the same dose will result in a greater degree of exposure in older patients.

Muscle symptoms

The most common adverse effects that limit treatment with statins are muscle symptoms. These include myalgia, myositis and rhabdomyolysis (Table 1). The risks of muscle symptoms are related to the dose of the statin.

The risk of muscle damage with statins increases with age over 70 years, and with age-associated factors such as multiple medicines use, comorbidity and sarcopenia (low skeletal muscle mass and function) (Table 2).

Table 1. Muscle symptoms associated with statins

Condition	Clinical presentation	Prevalence
Myalgia	Musculoskeletal pain without creatinine kinase increase	5–10% of patients in clinical trials
Myositis	Muscle symptoms with elevated creatinine kinase	0.1–0.2% of patients in clinical trials
Rhabdomyolysis	Severe muscle symptoms with creatinine kinase greater than 10 times the upper limit of normal, complicated by myoglobinuria and impaired renal function	Rare

Table 2. Age-associated factors that increase the risk of rhabdomyolysis with statins

Risk factor	Mechanism	Association with old age
Concomitant medicines	Pharmacokinetic drug – drug interactions increase exposure to statins (vary between statins) Pharmacodynamic interactions with other drugs that cause myopathy	Increased prevalence of polypharmacy
Comorbidity		
Renal and hepatic impairment	Increased exposure to statins	Decreased renal and hepatic function in old age
Hypothyroidism	Also causes myopathy	Increased prevalence and difficult clinical diagnosis in old age
Severe inter-current illness	Impaired metabolism results in increased exposure to statins and may also cause myopathy	Increased prevalence in old age
Low body weight	Increased exposure to statins and lower muscle mass	Weight decreases, particularly muscle mass, in old age and frailty

Adapted from Statins, macrolides and rhabdomyolysis. Medicines Safety Update No 5. Therapeutic Goods Administration; 2010 Oct.

Statin myopathy is likely to have a greater impact in older people, with limited musculoskeletal reserve, than in younger people, who generally have more muscle mass and strength and better mobility.

Liver enzyme increases

Elevated hepatic transaminases occur in 0.5-2% of patients treated with statins and are dose-dependent. Their clinical significance is uncertain and progression to liver failure is very rare. The transaminases may normalise if the statin dose is reduced and elevation does not always recur if the patient resumes the statin.[13] The effect of ageing on the risk of hepatic damage with statins is not known. In old age the risk of drug-induced liver injury appears to increase for some drugs, such as non-steroidal anti-inflammatory drugs, and decrease for others such as paracetamol. While drug-induced liver injury is commonly defined as moderate with an increase in liver enzymes over 2.5 times the upper limit of normal and severe at 5 times the upper limit of normal, these thresholds may be lower in older people because of their 30% decrease in liver mass.

Other adverse effects

The commonest adverse effects observed with statins are gastrointestinal, such as abdominal pain, constipation and nausea. A rare but serious adverse event is reversible peripheral neuropathy.

An increased risk of diabetes with statins was recently reported. Diabetes has also been found to be more common in older patients and those taking higher dose and higher potency statins.[14]

Studies have reported reversible cognitive impairment with statin use, both in patients with previously intact cognition and in those with pre-existing cognitive impairment.[15-17] This prompted the US Food and Drug Administration to change the prescribing information for statins* and has been noted by the Australian Therapeutic Goods Administration.†

A recent randomised controlled trial in younger patients suggested that compared to placebo, those prescribed statins were more likely to report a loss of energy and worsening exertional fatigue over six months of treatment.[18] This effect may have considerable impact on older patients with less functional reserve.

Drug interactions

Gemfibrozil is the drug most commonly associated with statin-induced myopathy. When taken concomitantly it inhibits the hepatic uptake of statins (via the organic anion transporter poly-peptide 1B1) and their biotransformation by glucuronidases. There is a smaller increase in the risk of myopathy with co-administration of other fibrates and statins because this pharmacokinetic interaction does not occur. The metabolism of atorvastatin and simvastatin is inhibited by cytochrome P450 3A4 inhibitors (for example macrolide antibiotics, amiodarone), increasing the risk of adverse effects (see Drug interactions: Fatal rhabdomyolysis following voriconazole and simvastatin, Aust Prescr 2012;35:88-9).

When should treatment be stopped?

When healthcare professionals and patients agree that there is no clinical benefit of treatment or the risks are greater than any potential benefit, treatment should be stopped. Withdrawal or deprescribing of statins should be considered when:

- the potential benefits are no longer clinically relevant. In patients with severe physical or cognitive impairments, or those in their last year of life, therapeutic aims often change from preventative to palliative and reducing the risk of vascular events or mortality may not be relevant.
- patients have serious adverse effects such as myositis, rhabdomyolysis or severe hepatic failure
- patients have symptoms or signs consistent with adverse effects in a temporal pattern consistent with statin exposure, such as myalgia, moderate or severe elevation of hepatic enzymes, cognitive impairment or fatigue
- patients need medicines that interact with statins (increasing the risk of toxicity).

Good opportunities to discuss withdrawal of statins include comprehensive health assessments by general practitioners or specialists, assessments on admission to or discharge from hospital or on entry to residential aged-care facilities, and after medication reviews by accredited pharmacists.

Conclusion

Evidence supports statin use for secondary prevention of coronary heart disease in older adults. However, this age group has an increased risk of adverse events from statins, particularly myopathy. The effect of these drugs on frailty, disability and institutionalisation is not well established. They are likely to decrease the risk of these outcomes by preventing vascular events, but to increase the risk by causing myopathy.

Randomised trials in older people (frail and robust) with clinically relevant endpoints are required to inform therapy in this large and growing patient population. Management of older adults relies on extrapolation of the available evidence and frequent reassessment as the patient's physiology, pathology, function and priorities change over time.

Acknowledgement

Danijela Gnjidic is supported by a National Health and Medical Research Council Early Career Fellowship.

*www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm293623.htm [cited 2013 May 3]

†www.tga.gov.au/safety/alerts-medicines-statins-120302.htm [cited 2013 May 3]

References

1. Morgan TK, Williamson M, Pirotta M, Stewart K, Myers SP, Barnes J. A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. Med J Aust 2012;196:50-3.
2. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med 1993;153:1065-73.
3. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370: 1829-39.
4. Afilalo J, Duque G, Steele R, Jukema JW, De Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical Bayesian meta-analysis. J Am Coll Cardiol 2008;51:37-45.
5. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
6. Lacroix AZ, Gray SL, Aragaki A, Cochrane BB, Newman AB, Kooperberg CL, et al. Statin use and incident frailty in women aged 65 years or older: prospective findings from the Women's Health Initiative Observational Study. J Gerontol A Biol Sci Med Sci 2008;63:369-75.
7. Gnjidic D, Le Couteur DG, Blyth FM, Travison T, Rogers K, Naganathan V, et al. Statin use and clinical outcomes in older men: a prospective population-based study. BMJ Open 2013;3:e002333 .
8. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2009;2:CD003160.
9. McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. Cochrane Database Syst Rev 2010;8:CD007514 .
10. Padala KP, Padala PR, McNeilly DP, Geske JA, Sullivan DH, Potter JF. The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study. Am J Geriatr Pharmacother 2012;10:296-302.
11. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423.
12. Zhou Z, Rahme E, Abrahamowicz M, Tu JV, Eisenberg MJ, Humphries K, et al. Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect. CMAJ 2005;172:1187-94.
13. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Circulation 2002;106:1024-8.
14. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, De Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735-42.
15. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy 2009;29:800-11.
16. King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW. Cognitive impairment associated with atorvastatin and simvastatin. Pharmacotherapy 2003;23:1663-7.
17. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871-80.
18. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. Arch Intern Med 2012;172:1180-2.

Further reading

1. Smith J. Appropriate primary prevention of cardio-vascular disease: does this mean more or less statin use? Aust Prescr 2011;34:169-72.

Conflict of interest: none declared

Sarah Hilmer, *Staff Specialist* [1], *Associate Professor* [2], **Danijela Gnjidic**, *Lecturer*[3], *Research fellow*[1–4],

[1]*Departments of Clinical Pharmacology and Aged Care, Royal North Shore Hospital, Sydney,* [2]*Sydney Medical School University of Sydney,* [3]*Faculty of Pharmacy, University of Sydney,* [4]*Centre for Education and Research on Ageing Concord Hospital Sydney.*

This article is reproduced from the *Australian Prescriber* 2013; **36**: 79-82, by prior arrangement, courtesy of *Australian Prescriber*.

ISSN 1391-0736

Printed by Ananda Press, Colombo.